EXHIBIT C

Modifying BITTERNESS

Mechanism, Ingredients, and Applications

Edited by

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in fact only large doses cause GI problems, nervousness, stupor, convulsions and finally death. Vermouth is a blend of white wines containing traces of absinthium and other flavors. The bitter components, mainly azulenoids, may be removed by gel permeation chromatography on cross-linked dextran oxypropyl ether gel such as Sephadex LH-20 (Kodama et al., 1992a, 1992b, 1992c).

The pH-sensitive polymethyacrylate (Eudragit resin) microcapsules were suitable for taste masking of antibiotics (Friend, 1992a, 1992b). A polymer carrier system was developed to reduce the bitterness of erythromycin and its 6-*O*-methyl derivative, clarithromycin, by adsorption to Carbopol (R.I.T.A. Corp., Woodstock, IL). The mechanism involves ionic bonding of the amine macrolide to the high molecular weight polyacrylic acid, thereby removing the drug from the solution phase in an ion-free suspension. After ingestion, endogenous cations displace the drug from the polymer into the gastrointestinal tract to achieve bioavailability (Lu et al., 1991).

Poly(vinyl acetal) (diethylamino)acetate is soluble in gastric juice and organic solvents. Hence, it is used as a coating polymer to prevent water entry into tablets and to mask drug bitterness. In aqueous 10% solution with increasing temperature, the solution coagulates hydrophobically to form a hydrogel. The gel formation impacts the thermo shrinking and drug-dissolution properties of clarithromycin, and a large study identified critical ratios of clarithromycin in the gel to optimize the degree of microencapsulation giving efficacy and taste masking (Shimano et al., 1994). Clarithromycin was also dispersed in cacao fat at 35–50°C and atomized to give fine granules, which were suspended in 7 wt% of poly (vinyl acetal) (diethylamino)acetate at 0°C and spray-dried. The preparation has no bitter taste and good bioavailability (Koyama et al., 1990a).

Oral preparations are manufactured by soaking particles containing water-soluble biologically active compounds encapsulated in polymers in buffer solutions containing carboxylic acids and metal hydroxides. An aqueous suspension contained water 94, poly(vinyl acetal) (diethylamino) acetate 5, sodium lauryl sulfate 0.02, cetyl alcohol 0.005 and clarithromycin 1 wt. part. The mixture was sprayed through a nozzle to give aqueous particles, which were soaked in glycine buffer containing sodium hydroxide at 52° for 14 h and dried at 7° for 30 min. to give a nonbitter oral preparation (Koyama and Shimano, 1993a). Similar formulations are given to prepare an aqueous clarithromycin gel that is not bitter (Koyama and Shimano, 1993b).

β-Lactam antibiotics having basic groups may have their unpleasant odor and bitter taste masked while still retaining excellent dissolution properties and absorbability of the active ingredient. Water-soluble enteric polymers and ion-exchange resins provide masking potential in granules